PATENT
Attorney Docket No. A-64260-5/DJB/RMS/AMS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Not Assigned
NOLAN	Group Art Unit: Unknown
Serial No. Unknown	San Francisco, California
Filed: Herewith	
For: Methods for Screening for Transdominant Intracellular Effector Peptides and RNA Molecules	

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I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231.
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SIGNED

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Prior to substantive examination please amend the above-referenced application as indicated below.

The Commissioner is authorized to charge any fees including extension fees or other relief which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-64260-5/DJB/RMS/AMS).

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In the Claims:

Please cancel claims 1-22, without prejudice or disclaimer.

Please add the following new claims:

--23. A method for in vitro screening for a transdominant intracellular bioactive agent capable of altering the phenotype of a cell, said method comprising the steps:

a) introducing a molecular library of biased randomized candidate nucleic acids into a plurality of cells, wherein each of said nucleic acids comprises a different nucleotide sequence, wherein said biased randomized candidate nucleic acids are biased to minimize stop codons, and wherein said randomized candidate nucleic acids are expressed in said cells to produce a plurality of randomized peptides;

b) screening said plurality of cells for a cell exhibiting an altered phenotype, wherein said altered phenotype is due to the presence of a transdominant bioactive agent; and

c) identifying said transdominant bioactive agent.

24. A method for in vitro screening for a transdominant intracellular bioactive agent capable of altering the phenotype of a cell, said method comprising the steps:

a) introducing a molecular library of biased randomized candidate nucleic acids into a plurality of cells, wherein each of said nucleic acids comprises a different nucleotide sequence, wherein said biased randomized candidate nucleic acids are biased to interact with a class of molecules and wherein said randomized candidate nucleic acids are expressed in said cells to produce a plurality of randomized peptides;

b) screening said plurality of cells for a cell exhibiting an altered phenotype, wherein said altered phenotype is due to the presence of a transdominant bioactive agent; and

c) identifying said transdominant bioactive agent.

25. A method according to claim 23 or 24 further comprising the step:

d) isolating said cell exhibiting an altered phenotype.

26. A method according to claim 25 further comprising the step:

e) isolating said candidate nucleic acid from said cell.

27. A method according to claim 26 further comprising the step:

f) isolating a target molecule using

i) said candidate nucleic acid; or

ii) the expression product of said candidate nucleic acid.

28. A method according to claim 23 wherein said biased randomized candidate nucleic acids comprise codons comprising NNK, wherein N is selected from the group consisting of A, T, C and G, and K is selected from the group consisting of T and G.

29. A method according to claim 24 wherein said biased randomized candidate nucleic acids are biased to interact with a class of molecules selected from the group consisting of SH3 domains, SH2 domains, death domains, enzyme inhibitors, enzyme substrates and protease cleavage sites.

30. A method according to claim 23 or 24 wherein said nucleic acids further comprise a presentation sequence capable of presenting said expression product in a conformationally restricted form.

31. A method according to claim 23 or 24 wherein said introducing is with retroviral vectors.

32. A method according to claim 23 or 24 wherein said cells are mammalian cells.

33. A method according to claim 23 or 24 wherein said library comprises at least 10^4 different nucleic acids.

34. A method according to claim 23 or 24 wherein said library comprises at least 10^5 different nucleic acids.

35. A method according to claim 23 or 24 wherein said library comprises at least 10^6 different nucleic acids.

36. A method according to claim 23 or 24 wherein said library comprises at least 10^7 different nucleic acids.

37. A method according to claim 23 or 24 wherein said library comprises at least 10^8 different nucleic acids.

38. A method according to claim 23 or 24 wherein each of said candidate nucleic acids is linked to nucleic acid encoding at least one fusion partner.

39. A method according to claim 38 wherein said fusion partner is a presentation sequence capable of presenting said expression product in a conformationally restricted form.

40. A method according to claim 38 wherein said fusion partner is a rescue sequence.

41. A method according to claim 38 wherein said fusion partner is a stability sequence.

42. A method according to claim 38 wherein said fusion partner is a dimerization sequence.

43. A method according to claim 38 wherein said fusion partner is a targeting sequence.

44. A method according to claim 43 wherein said targeting sequence is selected from the group consisting of:

a) a localizing signal sequence capable of constitutively localizing said translation product to a predetermined subcellular locale;

b) a membrane-anchoring sequence capable of localizing said translation product to a cellular membrane; and

c) a secretory signal sequence capable of effecting the secretion of said translation product.

45. A method according to claim 44 wherein said targeting sequence is a nuclear localization signal (NLS).

46. A method according to claim 44 wherein said targeting sequence is a myristylation sequence.

47. A molecular library of retroviruses comprising at least 10^5 different biased randomized nucleic acids encoding a plurality of biased randomized peptides, wherein said biased randomized candidate nucleic acids are biased to minimize stop codons.

48. A molecular library of retroviruses according to claim 47 comprising at least 10^6 different biased randomized nucleic acids encoding a plurality of biased randomized peptides.

49. A molecular library of retroviruses according to claim 47 comprising at least 10^7 different biased randomized nucleic acids encoding a plurality of biased randomized peptides.

50. A molecular library of retroviruses according to claim 47 comprising at least 10^8 different biased randomized nucleic acids encoding a plurality of biased randomized peptides.

51. A cellular library of mammalian cells containing a molecular library of retroviral constructs, said molecular library comprising at least 10^5 different biased randomized nucleic acids encoding a plurality of biased randomized peptides, wherein said biased randomized candidate nucleic acids are biased to minimize stop codons.

52. A cellular library according to claim 51 wherein said constructs are integrated into the cellular genome.

53. A molecular library of retroviruses according to claim 47, wherein said nucleic acids further encode a fusion partner.

54. A molecular library of retroviruses according to claim 53, wherein said fusion partner comprises a targeting sequence.

55. A molecular library of retroviruses according to claim 53, wherein said fusion partner comprises a rescue sequence.

56. A molecular library of retroviruses according to claim 53, wherein said fusion partner comprises a stability sequence.

57. A molecular library of retroviruses according to claim 53, wherein said fusion partner comprises a dimerization sequence.

58. A molecular library of retroviruses according to claim 47, wherein said randomized nucleic acids are biased in their randomization.--

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REMARKS

The present application is a continuation of U.S. Serial No. 09/727,715, filed November 28, 2000. The application has been amended from the original submission to comply with 37 C.F.R. § 1.821-1.825, and to include an amended priority statement under C.F.R. § 1.78(a)(2). This application contains no new matter over the originally submitted application.

New claims 23-58 are pending. Claims 23-27 and 30-46 are identical to issued claims 1-22 of U.S. Patent No. 6,153,380, (a parent of the present application), with the additional elements of "identifying said transdominant bioactive agent" and either "said biased randomized candidate nucleic acids are biased to minimize stop codons" (claim 23), or "said biased randomized candidate nucleic acids are biased to interact with a class of molecules" (claim 24). Support for the new elements is found throughout the specification and as further described. Support for "identifying said transdominant bioactive agent" in claims 23 and 24 is at p. 34, lines 13-25. Support for "said biased randomized candidate nucleic acids are biased to minimize stop codons" in claim 23 is found at p. 21, lines 4-7. Support for "said biased randomized candidate nucleic acids are biased to interact with a class of molecules" in claim 24 is found at p. 21, lines 20-21.

Support for claims 28-29 and 47-58 is found throughout the specification and as further described. Support for claim 28 is found at p. 21, lines 4-5. Support for claim 29 is found at p. 22, lines 9-12. Support for claims 47-58 is found at p. 3, line 28 to p. 4, line 2; p. 6, lines 5-6 and lines 12-19; p. 19, lines 30-31; p. 20, lines 25-28; and p. 23, lines 19-20.

Applicants respectfully submit that the claims are in condition for allowance, and an early notification of such is respectfully requested. Please direct any calls in connection with this application to the undersigned attorney.

Respectfully submitted,

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